Review Article

Obstetric Medicine

Obstetric Medicine
2015, Vol. 8(4) 168–171

DOI: 10.1177/1753495X15600572
obm.sagepub.com

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Insomnia and sleep deficiency in pregnancy

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Abstract

Insomnia and sleep deficiency in pregnancy are very common with most women reporting sleep disturbances during pregnancy. Insomnia and sleep deficiency are also more prevalent as pregnancy progresses, possibly related to pregnancy-related physical symptoms or discomfort. There is increasing evidence indicating that these sleep problems may be associated with adverse maternal and fetal outcomes such as depressive symptoms, increased pain during labor, more Caesarean sections, preterm birth, and low birth weight. Treatment of insomnia remains challenging as some of the more commonly used sleep inducing medications such as benzodiazepines and hypnotic benzodiazepine receptor agonists may be associated with adverse neonatal outcomes. Nonpharmacological treatments such as cognitive behavioral therapy are available but the data in pregnancy are often lacking.

Keywords

Pregnancy, insomnia, adverse outcomes, therapy

Date received: 5 May 2015; accepted: 22 July 2015

Pregnancy is associated with many physical, hormonal, and physiological changes which may influence sleep; 66 to 94% of women report sleep disturbances during pregnancy, one manifestation of which is insomnia.[1,2] Insomnia is defined as one or more of the following: difficulty initiating or maintaining sleep, waking from sleep too early, and/or the complaint of nonrestorative sleep.[3] Sleep deficiency, another common complaint, is inadequate amount of sleep, with normal sleep outside pregnancy being 7 to 9 h of sleep a night.

Sleep across trimesters

During the first trimester, sleep increases (on average 7.4 to 8.2 h) and then decreases in the third trimester (6.6 to 7.8 h) as evidenced by surveys[4,5] as well as polysomnography.[6] The rate of sleep disturbances also changes across trimesters, ranging from 13% in the first trimester, 19% in the second, and 66% in the third[1]. At the beginning of pregnancy, the incidence of insomnia is lower at 12.6%[7] and then increases as pregnancy progresses.[5,8] Up to 73.5% of women display some degree of insomnia at a median of 39 weeks, further classified as mild in 50.5%, moderate 15.7%, and severe in 3.8%.[9] In the last trimester of pregnancy, up to 69.9% reported difficulty in maintaining sleep, 34.8% described early morning awakenings, and 23.7% reported difficulty falling asleep.[10]

In the first trimester, the most common causes of poor sleep are nausea/vomiting, urinary frequency, and backache, while in the second and third trimesters the causes are fetal movements, heartburn, cramps or tingling in the legs, and shortness of breath.[1,8,11,12] Night waking is the most common sleep disturbance; by the end of pregnancy almost all women are waking up[4,8] and for longer periods of time[8].

Pregnant women do not always see their sleep as being a problem; 97% of 127 pregnant women surveyed reported symptoms of disrupted sleep, but only a third of them identified themselves as having a sleep disorder[11]. Sleep disturbances are more commonly associated with pre-existing and de-novo depression[13–15] as well as smoking.[9] Insomnia generally worsens right before labor because of the secretion of oxytocin, a wake promoting hormone.[16] Why some women are more susceptible to insomnia is unclear. According to a cognitive model of insomnia,[17] in women who have tendency to worry or be anxious, some of the typical sleep changes in pregnancy may be expressed with a higher level of severity.[18] Hormonal changes also play a role. The higher levels of estrogen and progesterone are thought to contribute to insomnia and they also influence other hormones such as the cortisol-melatonin ratio.[19] Because progesterone and cortisol share binding sites on corticosteroid-binding globulin, this leads to higher free cortisol which may increase arousal.[20]

Diagnosing insomnia and sleep disturbances

A diagnosis of insomnia is usually made via self-report sleep history.[21] Sleep diaries can also provide information about bedtime, sleep onset, nighttime awakenings, awake time, and subjective evaluation of sleep quality.[22] Overnight polysomnograms are rarely needed to diagnose insomnia. There are also sleep questionnaires available which are mostly used for research purposes and not necessary for the diagnosis of insomnia. The Pittsburgh Sleep Quality Index (PSQI) measures quality and patterns of sleep,[23] and it seems to be a reliable and valid tool in pregnant women.[24] It includes seven items related to sleep disturbance severity, sleep-related satisfaction and the degree of daytime functional impairment, impairment perception and distress and concern-related to sleeping problem. Each item is rated on a five-point Likert scale (0–4) and added up to a total score ranging from 0 to 28, with scores higher than 8, suggesting insomnia. The insomnia severity index which uses seven items to examine the patient's perception of insomnia has not been specifically validated among pregnant women.[25] The insomnia symptoms questionnaire which is a 13-item self-report questionnaire was recently validated in 143 pregnant women at 12 weeks gestation.[7]

Consequences of insomnia

In the general population, there is increasing evidence that abnormal sleep patterns may be associated with adverse outcomes such as cardiovascular disease and mortality.[26,27] In pregnancy, Palagini et al.[28] hypothesise that sleep loss may be a result of stress as well as a stressor itself, therefore affecting both the hypothalamic-pituitary-adrenal axis

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(and possibly fetal exposure to stress hormones) and the proinflammatory system which may in turn lead to adverse pregnancy outcomes. Sleep disturbances such as short sleep duration and poor sleep efficiency as measured by the PSQI and sleep diaries in mid to late pregnancy have been shown to be associated with increased levels of interleukin 6,[29] C-reactive protein,[30] and an increased inflammatory state.

Short sleep as assessed by sleep questionnaires may increase the risk of gestational diabetes (GD) with a relative risk ratio of 5.6 among women sleeping ≤4 h a night versus 9 h/ night.[31] Sleep duration as measured by sleep questionnaires is also inversely correlated with glucose values ($r = -0.21$, $p < 0.001$): each hour of reduced sleep time is associated with a 4% increase in glucose and sleep duration of less than 7 h/night increased the risk of GD.[32] These studies are based on subjective rather than objective data. Sleep duration of ≤6 h/night in early pregnancy is associated with increased mean 3rd trimester blood pressure.[33]

Poor sleep quality may be a risk factor for developing depressive symptoms during pregnancy.[24,34] Together with reduced sleep, poor sleep quality may affect women's ability to cope with labor pain.[35] Less total sleep time as measured by actigraphy the night before hospitalization may be associated with elevated perception of pain and discomfort during labor.[36] If women sleep less than 6 h a night compared with an average of over 7 h of sleep during the last month of pregnancy as measured by 48 h wrist actigraphy and sleep questionnaires, they are at increased risk for longer labors, 4.5 times more Caesarean sections and more spontaneous preterm deliveries.[37,38] Poor sleep is also associated with an increased risk of emergency cesarean section (OR 1.57, 95% CI 1.14–2.16).[39] Poor sleepers are 20% more likely to undergo a cesarean section and have a longer labor.[40] In 457 patients who answered sleep questionnaires, those who slept more than 8 h a night had a shorter first stage of labor of 6 to 10 h vs. ≥10 h ($p = 0.029$) and most of the neonates born to women who slept more than 8 h had Agpar score >9 ($p = 0.001$).[41] Most of the mothers with refreshing sleep has neonates weighted ≥2500 g ($p < 0.001$).[41] Sleep duration less than 8 h increases the risk of low birth weight (OR 2.84, 95% CI 1.49–5.40).[42]

Women with sleep deprivation (≤5 h per night) are at higher risk of preterm births (1.7 (CI 1.1–2.8)), with the highest risk observed for medically indicated preterm births (2.4 (CI 1.0–6.4)).[43] Earlier data from 1990 examining the outcomes of pregnancy during residency in female physicians versus the wives of their male counterparts showed that working long hours was associated with increased preterm labor but not preterm delivery.[44] Poor sleep quality is also a predictor of preterm birth, with the largest effects in early pregnancy (14–16 weeks OR 1.25 95% CI (1.04–1.50), $p = 0.02$). With every one-point increase on the PSQI in early and later pregnancy, the odds of preterm birth increased 25% and 18% respectfully.[45] Sleep latency as measured subjectively is also significantly increased in pregnant women who deliver preterm.[46]

Pharmacological treatment of insomnia in pregnancy

Four and a half percent of pregnant women admit to the use of sleep medication and 1.9% of natural remedies.[10] This varies by trimester: 0.9% in the first trimester, 0% during the second trimester, and 2.2% during the third trimester.[4] A recent review article was published on the sleep-promoting medications used in pregnancy.[47]

Benzodiazepines such as alprazolam, clonazepam, diazepam, lorazepam, and temazepam enhance the effect of neurotransmitter gamma-aminobutyric acid (GABA) at the GABAa receptor and this results in sedative effect.[48] Hypnotic benzodiazepine receptor agonists (zaleplon, zolpidem and eszopiclone) are nonbenzodiazepines drugs which act on the GABAa receptor. They are the most commonly prescribed drugs for insomnia including in pregnant women.[49]

All these agents can cross the placenta and may cause adverse effects.[48] In their recent review article, Okun et al.[47] summarized seven studies including one prospective cohort study in which 411 pregnant women who reported first trimester use of alprazolam were followed through delivery.[50] These studies showed no significant increased risk for congenital malformations. There have been reports of "floppy infant syndrome" in babies born to mothers taking diazepam long-term during pregnancy and there is also a concern for neonatal withdrawal symptoms with benzodiazepines.[51]

Multiple studies have examined the use of hypnotic benzodiazepine receptor agonists in pregnancy, most of which reported no significant adverse outcomes including congenital malformations, preterm birth, and/or low birthweight.[47] But in a retrospective cohort study from Taiwan, 2497 pregnant women who used zolpidem had an increased risk of low birthweight and/or small-for-gestational age infants, preterm and/or cesarean delivery when compared with 12,485 pregnant women who were not using zolpidem.[52] This study utilized the Taiwan National Health Insurance Dataset. It did not include a review of medical records and therefore could not account for the severity of insomnia, the other contributing factors such as tobacco and/ or alcohol use nor the adherence or nonadherence to zolpidem. A population-based retrospective cohort study of 390 Swedish pregnant women who were exposed to benzodiazepines and/or hypnotic benzodiazepine receptor agonists during late pregnancy also showed an increased risk of preterm and low birthweight.[53] This was again a registry study with its limitations; it did not account for maternal indication for drug use nor for alcohol use. Subsequent data from the Swedish Birth Registry on 1318 pregnant women who used benzodiazepine receptor agonists zaleplon (n = 32), zolpidem (n = 603), and zopiclone (n = 692) showed no increase in congenital malformations.[54] This registry captures maternal self-reported medication use from the initial visit with a midwife; it does not include timing, dose, and duration of the drug used. It also does not account for induced pregnancy terminations, which may underestimate the rate of congenital malformations.

Antidepressants are another class of drugs that are sometimes used for their sedating properties. They work through the monoamine neurotransmitters which include norepinephrine, dopamine, and serotonin which regulate sleep-wakefulness and sleep architecture.[55] In a randomly controlled trial of an antidepressant trazadone, an antihistamine or placebo in the treatment of insomnia in 54 age-matched pregnant patients at 26–30 weeks' gestation, trazadone increased sleep duration and sleep efficiency compared with placebo.[56] But this study did not address delivery or infant outcomes.[56] It also included diphenhydramine which is an antihistamine or H1 receptor antagonist. This class of drug is available over-the-counter and is widely used in pregnancy for symptoms besides insomnia such as nausea, vomiting, and cold/ allergy symptoms[57]; 92% of women reported using an over-the-counter sleep aid occasionally during their pregnancy.[58] Diphenhydramine was equally efficacious compared with the antidepressant trazadone for improving sleep quality and depressive symptoms compared with placebo.[56] Overall, data from the National Birth Defects Prevention study suggested that exposure to antihistamines in early pregnancy did not show any increased risk in cardiac effects, birth defects or major malformations.[57]

In summary, the sleep aids described above do not seem to confer an increased risk for congenital malformations, although benzodiazepines and hypnotic benzodiazepines receptor agonists may be associated with increased rates of preterm labor, cesarean delivery, and small-for-gestational-age and/or low birthweight infants. But it remains unclear what role insomnia itself is playing in the development of these adverse outcomes.

Nonpharmacological management of insomnia in pregnancy

Improving sleep hygiene (establishing regular sleep-wake cycles, avoiding naps and caffeine), stimulus control (going to bed only when sleepy and getting out of bed during prolonged awakenings), minimising fluid intake prior to bed to decrease nocturia, managing physical discomfort

using pillow support or local heat, cognitive behavioral therapy (CBT), exercise, and meditation may help insomnia.[59,60] A Canadian study in 2013 reviewed nonpharmacological interventions for insomnia during pregnancy.[61] Acupuncture, exercise, massage or relaxation therapy, and mindful meditation and prenatal hatha yoga may be beneficial for insomnia, but the studies are small and heterogeneous and therefore it is difficult to make a definite recommendation regarding these interventions in pregnant patients with insomnia.[61] When insomnia and depression coexist, an intervention composed of partial sleep deprivation and light therapy showed promise in 12 pregnant women for treating both insomnia and depression.[62]

CBT has been shown in nonpregnant patients to be safe, as effective as and more durable than sedative medications but data in pregnant women is lacking. CBT should improve sleep habits by identifying and changing the thoughts and the behaviors that are affecting the ability to allow the person to sleep or sleep well.[63]

Given the possible adverse outcomes of both insomnia and the available medications for treating insomnia in pregnancy, future studies could focus more on the nonpharmacologic means of treating insomnia especially CBT.

Conclusions

Insomnia and sleep deficiency are very common during pregnancy and may be associated with preterm birth, increased rate of cesarean sections, worse labor pain, and depression. Healthcare practitioners should be aware of the importance of adequate sleep, question their patients regarding their sleep quantity and quality (including environmental and behavioral factors), and discuss treatment options.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Guarantor

CR.

Contributorship

CR contributed all the work to this review article.

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